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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,988	06/13/2001	Charles R. Cantor	25491-2408	5954

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/880,988	Applicant(s) CANTOR ET AL.	
	Examiner Arun Chakrabarti	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8,10-20 and 25-45 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8,10-20 and 25-45 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Specification

1. Claims 4, 6, 17, 27, 28, 31, 33, 36, and 42 have been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-8, 10-20, and 25-27 are rejected under 35 U.S.C. 103 (a) over Brennan (U.S. Patent 5,174,962) (December 29, 1992) in view of Canard et al. (U.S. Patent 5,798,210) (August 25, 1998) further in view of Schulz (U.S. Patent 6,232,076 B1) (May 15, 2001).

Brennan teaches a method for identifying nucleotides at one or more base positions and determining the nucleotide sequence of a plurality of target nucleic acid molecules (Abstract, and Column 6, lines 12-23), comprising:

a) synthesizing extension products of the target nucleic acid in the presence of chain terminating nucleotides and mass-matched nucleotides (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Schemes D and E);

b) determining the mass of each extension product (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4);

c) calculating a mass shift from a period for the mass of each extension product (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Figure 2B),

whereby nucleotides at one or more base positions and the sequence is determined by identifying the nucleotide that corresponds to each mass shift (Column 6, lines 10-64).

Brennan also teaches a method for determining the nucleotide sequence of a plurality of target nucleic acid molecules by incorporating pair-matched nucleotides into the target nucleic acid (Abstract, and Column 6, line 65 to column 10, line 64).

Brennan inherently teaches a method for detecting different nucleotide base compositions in a population of nucleic acids having identical length and different base compositions with

respect to the difference of a single base (Column 11, lines 1-38, in this case DNA sequence of any genetic material and Figures 1-2) comprising:

a) synthesizing the nucleic acids in the presence of one or more nucleotide analogs to produce synthesized nucleic acids (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4, and Schemes D and E); and

b) determining a mass of each synthesized nucleic acid (Abstract, Column 5, line 25 to column 6, line 8, and Examples 1-4);

whereby different nucleotide base compositions are detected by determining the mass of each synthesized nucleic acid (Column 5, line 25 to column 6, line 8, and Examples 1-4, and Figure 2B),

wherein the nucleotide analog separates the masses of nucleic acids having different base compositions in a predetermined interval (Figures 1-2).

Brennan does not teach a method, wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates and there is a periodicity of the distribution of the extension products.

Canard et al. teach a method, wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates and there is a periodicity of the distribution of the extension products (Column 21, line 12 to column 22, line 67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the method of Brennan, the method

wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates of Canard et al. since Canard et al. state, "The use of hairpin primer makes it possible to use basic conditions for deprotection of the 3' hydroxyl compatible with a repetition of the procedure without addition of a primer at each step of the indirect determination of a nucleotide inserted. In fact, the rehybridization of the primer occurs intramolecularly and immediately (Column 4, line 66 to column 5, line 4)". An ordinary artisan would have been motivated by the express statement of Canard et al. to substitute and combine, within the method of Brennan, the method wherein the primers are plurality of duplex hairpin primers ligated to the single-stranded templates of Canard et al. in order to achieve the express advantages, as noted by Canard et al., of the use of hairpin primer, which makes it possible to use basic conditions for deprotection of the 3' hydroxyl compatible with a repetition of the procedure without addition of a primer at each step of the indirect determination of a nucleotide inserted and where the rehybridization of the primer occurs intramolecularly and immediately.

Brennan in view of Canard et al do not teach a method, wherein the chain-terminating nucleotide base pairs are mass-matched and have distinct molecular weights

Schulz teaches a method, wherein the chain-terminating nucleotide base pairs are mass-matched and have distinct molecular weights (Column 8, lines 16-36).

Brennan in view of Canard et al. do not teach a method, wherein the mass-matched deoxynucleotide is one and same and of identical length deoxyinosine.

Schulz teaches a method, wherein the mass-matched deoxynucleotide is one and same and of identical length deoxyinosine (Column 8, lines 16-36).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the method of Brennan in view of Canard et al, the method wherein the mass-matched deoxynucleotide is one and same and of identical length deoxyinosine of Schulz since Schulz states, "The polymerase extension product can also include other nucleotides which may be useful replacements for any of the above (deoxyadenosine, deoxyguanosine, deoxycytidine, deoxythymidine, etc) . Non limiting examples are deoxyinosine monophosphates (Column 8, lines 25-36)". An ordinary artisan would have been motivated by the express statement of Schulz to substitute and combine, within the method of Brennan, the method wherein the mass-matched deoxynucleotide is one and same and of identical length deoxyinosine of Schulz in order to achieve the express advantages, as noted by Schulz, of a nucleotide system which may be useful replacements for any of the deoxyadenosine, deoxyguanosine, deoxycytidine, deoxythymidine, etc.

4. Claims 28-45 are rejected under 35 U.S.C. 103 (a) over Brennan (U.S. Patent 5,174,962) (December 29, 1992) in view of Canard et al. (U.S. Patent 5,798,210) (August 25, 1998) further in view of Schulz (U.S. Patent 6,232,076 B1) (May 15, 2001) further in view of Shuber (U.S. Patent 5,888,778) (March 30, 1999).

Brennan in view of Canard et al. further in view of Schulz teaches a method of claims 1-8, 10-20, and 25-27 as described above including determining the mass of the extended nucleic acids by mass spectrometry.

Brennan in view of Canard et al. further in view of Schulz do not teach a method for detecting a mutation in a target nucleic acid sequence in a target nucleic acid molecule, in a sample, comprising:

a) hybridizing a nucleic acid molecule a primer to nucleic acid molecule in the sample, thereby producing a hybridized primer and a molecule from the sample;

wherein the primer is complementary to a sequence in the target nucleic acid that is adjacent to the region suspected of containing a mutation sequence;

b) contacting the hybridized primer with a composition comprising mass-matched deoxyribonucleoside triphosphates and a chain terminating nucleotide selected from a dideoxyribonucleoside triphosphate, such that the hybridized primer is extended until a chain terminating nucleotide is incorporated, thereby producing an extended primer ; and

c) determining the mass of the extended primer by mass spectrometry, thereby determining whether a mutation is present in the target nucleic acid sequence.

Shuber teaches a method for detecting a mutation in a target nucleic acid sequence in a target nucleic acid molecule, in a sample (Abstract), comprising:

a) hybridizing a single or plurality of primers to nucleic acid molecule in the sample, thereby producing a hybridized primer and a molecule from the sample (Column 7, lines 38-42);

wherein the primers are complementary to a sequence in the target nucleic acid that is adjacent to the region suspected of containing a mutation sequence (Column 7, lines 38-59, and Claims 1, 10, and 13);

b) contacting the hybridized primer with a composition comprising mass-matched deoxyribonucleoside triphosphates and a chain terminating nucleotide selected from a dideoxyribonucleoside triphosphate, such that the hybridized primer is extended until a chain terminating nucleotide is incorporated, thereby producing an extended primer (Column 7, lines 38-59, and Claims 1, 10, and 13);

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine, within the mass spectrometric method of Brennan in view of Canard et al. further in view of Schulz , the method of single and multiple primers designed to detect mutation of Shuber since Shuber states, "Moreover, due to their increased selectivity for target, methods of the invention may be used to detect and identify a target nucleic acid that is available in small proportion in a sample, and that would normally have to be amplified by, for example, PCR in order to be detected (Column 7, lines 56-59)". An ordinary artisan would have been motivated by the express statement of Shuber to substitute and combine, within the mass spectrometric method of Brennan, the method of single and multiple primers designed to detect mutation of Shuber in order to achieve the express advantages, as noted by Shuber, of an invention which due to their increased selectivity for target may be used

to detect and identify a target nucleic acid that is available in small proportion in a sample, and that would normally have to be amplified by, for example, PCR in order to be detected.

Response to Amendment

5. In response to amendment, 112 (second paragraph) and 102(b) rejections have been withdrawn. However, new 103(a) rejections based on the same prior art have been included.

Response to Arguments

6. In response to argument, 112 (second paragraph) and 102(b) rejections have been withdrawn.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Canard et al. since Canard et al. state, "The use of hairpin primer makes it possible to use basic conditions for deprotection of the 3' hydroxyl compatible with a repetition of the procedure without addition of a primer at each step of the indirect determination of a nucleotide inserted. In fact, the rehybridization of the primer occurs

intramolecularly and immediately (Column 4, line 66 to column 5, line 4)". This logic is applicable to all other motivations to combine the references.

In view of the response to arguments, new 103(a) rejections based on the same prior art have been included.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CAR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CAR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

Arun Chakrabarti,

Patent Examiner,

September 23, 2002